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Chapter 8

A Practical Way to ISO/GUM Measurement Uncertainty for Analytical Assays Including In-House Validation Data

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72048

Abstract

In this contribution, we outline the estimation of measurement uncertainty of analytical assays in a practical way, according to the so-called reconciliation paradigm, by considering the heritance of uncertainties according to the ISO Guide to the expression of uncertainty in measurement (ISO/GUM) approach and the accuracy (bias and precision) study coming from the in-house method validation. A cause and effect analysis is performed by using the Ishikawa diagram or fishbone plot, consisting of a hierarchical structure reaching a final outcome that is the analytical result. The procedure is illustrated with a case study. This procedure may be very suitable for processing data in accreditation of routine assays.

Keywords: ISO/GUM approach, method validation, uncertainty measurement

1. Introduction

The quality of analytical results is crucial because future decisions will be based on them. Uncertainty [1] is a good indicator of this quality. For example, two measurements made with the same ruler on different days by different people would be equivalent depending on their individual uncertainties.

Quality assurance measurements are a formal requirement in most of the analytical laboratories. As a consequence, to ensure that laboratories provide quality data, they are under continuous pressure to demonstrate their fitness for purpose, i.e., by giving confidence levels on the results. Measurement uncertainty will show the degree of agreement among results.

This concept of measurement uncertainty will be applicable to many cases, besides of quality control and quality assurance in production, such as complying with and enforcing laws and regulations, conducting a basic research, calibrating standards and instruments or developing, maintaining, and comparing international and national physical reference standards.

The ISO Guide to the expression of uncertainty in measurement, also known as the ISO/GUM or "bottom-up" [1], is one of the best approaches to estimate the uncertainty of analytical procedures. This procedure, originally conceived for use in physical measurements, has been suitably adapted to chemical ones in the EURACHEM/CITAC (Cooperation on International Traceability in Analytical Chemistry) guide [2] "Traceability in Chemical Measurement." However, this approach is tedious, time-consuming and unrealistic from the analytical viewpoint because their principles are significantly different from current procedures applied in analytical chemistry dealing with matrix effects, sampling operations and interferences [3, 4]. A strategy for reconciling the information requirements of ISO/GUM approach and the information coming from in-house method validation has been described by Ellison and Barwick [5]. The use of "cause" and "effect" analysis is the key for estimating the uncertainty of an analytical assay. In practice, this approach is performed by using a cause and effect diagram called Ishikawa or fishbone plot [6], consisting of a hierarchical structure that culminates in the "analytical result." In order to carry out the cause and effect analysis, the specification equation for the result is of utmost importance. The factors appearing in the equation (that contribute to the uncertainty of the result) are the main branches of the fishbone plot. For each branch, secondary factors can be considered, and so on, until their contribution to the result uncertainty is negligible. Two additional main branches (Recovery and Precision) come from the method validation. Nevertheless, these approaches exhibit some risks. The blind consideration of uncertainties coming from different sources of variation may lead to "double counting" in some instances. The analysts have to clearly identify the relationships among the sources of uncertainty in order to avoid duplications. Also, some sources of uncertainty that can be evaluated in a unique set of experiments must be suitably combined.

The combined uncertainty of the analytical measurand is the heritance of the uncertainties of all contributing variables (x_i) involved in the specification relationship where the value of measurand (Z) is defined as

$$Z = F(x_1, x_2, \ldots x_n) \tag{1}$$

Thus, the general expression for the combined uncertainty of measurand according to the law of propagation of uncertainty is given by

$$u^2(Z) = \sum_{i=1}^{n} \left(\frac{\partial F}{\partial x_i}\right)^2 u^2(x_i) + 2\sum_{i=1}^{n-1}\sum_{j=i+1}^{n} \left(\frac{\partial F}{\partial x_i}\right)\left(\frac{\partial F}{\partial x_j}\right) \operatorname{cov}\left(x_i, x_j\right) \tag{2}$$

When the specification function consists of products or ratios only, and the factors are considered to be independent, then

$$\begin{aligned} \left(\tfrac{u(Z)}{Z}\right)^2 &= \sum_{i=1}^{n} \left(\frac{u(x_i)}{x_i}\right)^2 \\ u_{rel}^2(Z) &= \sum_{i=1}^{n} u_{rel}^2(x_i) \end{aligned} \tag{3}$$

But this uncertainty does not consider the uncertainty contributions due to the intermediate precision of the assay and the trueness evaluated from recovery experiments. Nevertheless, it is possible to include these ones into the specification relationship either directly or by using unit-value factors $\left(f_i = 1 \pm u(f_i)\right)$ which do not contribute to the measurand value, but do contribute to its uncertainty [7, 8]. Accordingly, the modified specification relationship turns to:

$$Z = \frac{F(x_1, x_2, \ldots x_n)}{R} f_{prec} \tag{4}$$

The new involved parameters are the recovery, R, and the intermediate precision of the assay, f_{prec}. These contributions are issued from the data of method validation study. Accordingly, the uncertainty of measurand can be written as:

$$u_{rel}^2(Z) = \sum_{i=1}^{n} u_{rel}^2(x_i) + u_{rel}^2(R) + RSD_{prec}^2 \tag{5}$$

At this step, the considerations regarding to the sources of uncertainties have to be taken into account in order to avoid either under- or over-estimations of the result uncertainty.

The specification relationship involves a given set of parameters depending on the analytical procedure applied. Common factors are: mass determinations (obviously for sample weight and used standards), volumetric measurements (glassware and other devices delivering volume), analyte concentration coming from indirect calibration, and the precision and recovery of the analytical assay established in the validation study.

In the following, these factors will be outlined and their uncertainties will be discussed.

1.1. Uncertainty of sample mass

In a typical mass determination, the analytical balance is zeroed with the empty container on the pan, and the container is the filled and weighed. In this case, the uncertainty of mass measurements (without considering buoyancy) is given by [9]

$$u(m) = \sqrt{S_r^2 + S_{env}^2 + \frac{2}{3}a_L^2 + \frac{m^2 a_T^2 (\Delta T)^2}{9} + u_{CAL}^2} \tag{6}$$

where $S_r^2 + S_{env}^2$ is the variance of replication (repeatability and environmental variances) expressed as an weighting intermediate precision, a_L is the linearity specification of the balance, a_T is the sensitivity temperature coefficient, ΔT is the difference between the room temperature and the calibration temperature (20°C) and u_{cal} is the standard uncertainty for balance calibration.

Because the intermediate precision study is carried out for the entire analytical assay at the validation stage, individual contributions to the intermediate precision (here, weighting intermediate precision) cannot be taken into account for avoiding redundant counting of uncertainty. Thus, the uncertainty of mass will include the uncertainty contribution of lack

of linearity of balance, the uncertainty due to temperature effect and the calibration uncertainty

$$u(m) = \sqrt{\frac{2}{3}a_L^2 + \frac{m^2 a_T^2 (\Delta T)^2}{9} + u_{CAL}^2} \tag{7}$$

1.2. Uncertainty of glassware volume

As R. Kadis pointed out [10], the evaluation of uncertainty of volumetric measurements consists of three kinds of contributions: specification limits for the glassware of a given class, repeatability of filling the glassware to the mark and temperature effects. Again, in order to avoid double counting and uncertainty redundancy, the precision of filling the flask is not considered here; thus, the uncertainty in the volume measurement is given by

$$u(V) = \sqrt{\frac{a_{TOL}^2}{6} + \frac{\chi^2 V^2 (\Delta T)^2}{3}} \tag{8}$$

where a_{TOL} is the tolerance for a given class, χ is the dilatation coefficient for the filling liquid ($2.1 \times 10^{-4}\ K^{-1}$ for water), and ΔT as indicated earlier.

1.3. Uncertainty of concentration coming from calibration

Generally, in routine analysis, analytical determinations involve instrumental method where indirect calibration is applied. Common scenarios include external calibration, standard addition calibration (in case of matrix effects) and internal standard calibration (when intrinsic analytical signal variations appear or analyte losses may occur owing to sample preparation procedures [11]).

In case of linear calibration, the calibration straight line is established by preparing calibration standards. The primary stock standard solution is made by weighing the suitable mass of standard (m_{std}), of a given purity (P) in the corresponding volume of solvent (V_s)

$$C_{std} = \frac{m_{std} P}{V_s} \tag{9}$$

But this concentration has an uncertainty derived from the uncertainty in the weighting, in its purity and in the uncertainty of the glassware. The working standard solutions are prepared by diluting a volume (V_i) of the stock standard solution to a final volume V_f. So, the concentration of any calibration standard is given by

$$C_i = C_{std} \frac{V_i}{V_f} = \frac{m_{std} P V_i}{V_s V_f} \tag{10}$$

and has an uncertainty that can be suitably calculated. However, when applying ordinary least-squares techniques (simple linear regression), three requisites have to be fulfilled [12]:

- The independent variable x, is free from error $(\varepsilon(x) = 0)$ or at least, $\varepsilon(x) << \varepsilon(Y)$.
- The error associated to Y variable, is normally distributed, $N(0, \sigma^2)$.
- The variance of the Y variable, σ^2, remains uniform in the whole range of x (homoscedasticity).

In our case, the independent variable is the concentration of standard (C_i) and the Y variable is the analytical signal. In a typical case of multipoint calibration (external or internal), the three requirements mentioned above applies, and the ordinary least-squares procedure gives the calibration straight line $\widehat{Y}_i = b_0 + b_1 C_i$. The unknown analyte content is predicted from interpolation of the sample response signal Y_0 according to

$$C_{cal} = \frac{Y_0 - b_0}{b_1} \tag{11}$$

whose uncertainty can be estimated from the variance propagation law:

$$\begin{aligned} u^2(C_{cal}) &= \left(\frac{\partial C_{cal}}{\partial Y}\right)^2 u^2(Y_0) + \left(\frac{\partial C_{cal}}{\partial b_0}\right)^2 u^2(b_0) + \left(\frac{\partial C_{cal}}{\partial b_1}\right)^2 u^2(b_1) + 2\left(\frac{\partial C_{cal}}{\partial b_0}\right)\left(\frac{\partial C_{cal}}{\partial b_1}\right) \operatorname{cov}(b_0, b_1) \\ &= \frac{u^2(Y_0)}{b_1^2} + \frac{u^2(b_0)}{b_1^2} + \frac{(Y_0 - b_0)^2}{b_1^4} u^2(b_1) + \frac{(Y_0 - b_0)}{b_1^3} \operatorname{cov}(b_0, b_1) \\ &= \frac{u^2(Y_0)}{b_1^2} + \frac{u^2(b_0)}{b_1^2} + \frac{(Y_0 - b_0)^2}{b_1^4} u^2(b_1) - \frac{(Y_0 - b_0)}{b_1^3} \overline{C} u^2(b_1) \end{aligned} \tag{12}$$

where $\overline{C} = \frac{1}{N}\sum_i^N C_i$, N being the number of calibration points.

Eq. (10) can be rearranged to give the well-known formula recommended by EURACHEM [2]:

$$u(C_{cal}) = \frac{s_{y/x}}{b_1} \sqrt{\frac{1}{m} + \frac{1}{N} + \frac{\left(C_{cal} - \overline{C}\right)^2}{\sum_{i=1}^{N} \left(C_i - \overline{C}\right)^2}} \tag{13}$$

Here, $s_{y/x}$ is the residual standard deviation of the regression line, m is the number of replications measuring the sample signal and N the number of calibration points [13].

Aside from the calibration uncertainty, an additional uncertainty contribution can be considered from the preparation of standards as indicated in Eq. (8) and may be accounted separately in the uncertainty budget:

$$\frac{u^2(C_i)}{C_i^2} = \frac{u^2(m_{std})}{m_{std}^2} + \frac{u^2(P)}{P^2} + \frac{u^2(V_i)}{V_i^2} + \frac{u^2(V_s)}{V_s^2} + \frac{u^2(V_f)}{V_f^2} \tag{14}$$

Thus, the uncertainty of concentration is given by the uncertainty on sample analyte concentration coming from calibration, and the uncertainty due to the preparation of standards.

1.4. Uncertainty of the analytical assay from the in-house data of method validation (precision and trueness)

Intralaboratory assessment of method accuracy encompasses both precision and trueness study.

As EURACHEM guide advices [2], "the precision should be estimated as far as possible over an extended period of time." This may be accomplished by performing a between-day laboratory precision study. This precision study is carried out either by analyzing a typical sample, a quality control check sample or a validation standard [14] in "intermediate precision" conditions. Intermediate precision is the intralaboratory global precision under varied conditions as expected within a laboratory in a future assay. Accordingly, if a between-day precision study is carried out by spacing out the measurement days in such a way that the analysts, the apparatuses, glassware, stock solutions…really change, the precision estimation (from ANOVA) is a suitable "intermediate precision" estimation [14], leading to an evaluation of intermediate precision uncertainty, u_{IP}.

Again, according to EURACHEM [2], the trueness (bias) study can be performed

- by repeated analysis of a certified reference materials (CRM), using the complete measurement procedure;
- by comparing the results of analyzed samples against a reference method; and
- by applying recovery assays, using spiked placebos (validation standards) when available or spiked samples instead, and evaluating the recovery.

Thus, an estimation of the uncertainty of bias or recovery is calculated.

Both precision and trueness studies have to be carried out at least at three analyte concentration levels (low, medium and high) in order to cover the full range of analyte concentration indicated in the method scope.

In his excellent paper, Kadis [13] discussed the double counting risk in the uncertainty budget when calibration uncertainty is considered together with the precision uncertainty. The term $\frac{s_{x/y}}{b_1 m}$ in Eq. 13 features the estimated precision of the analyte concentration in the calibration experiment. The estimated precision (from in-house validation) considers all the sources of variability, including calibration, therefore the contribution of $\frac{s_{x/y}}{b_1 m}$ in the calibration uncertainty is redundant. Accordingly, the first term under the radical in Eq. (13) must be omitted to avoid double counting, or alternatively, the precision uncertainty can be omitted in the budget. Moreover, the recovery uncertainty includes the precision of the analyte mean value, which is used in the computation of recovery. Thus, some authors do not include the precision uncertainty together with the recovery uncertainty in the budget [13].

The use of cause and effect diagrams for designing the uncertainty budget including the in-house validation data is illustrated in the following worked example selected as case study.

http://dx.doi.org/10.5772/intechopen.72048

2. Fluorimetric determination of quinine in tonic water

This working example has been prepared from the papers of O'Reilly [15] and González and Herrador [14], and deals with the determination of quinine in tonic water samples from fluorescence measurements. Solutions that contain quinine in acid medium (0.05 M sulfuric acid) show fluorescence with a maximum excitation wavelength at 350 nm and a maximum emission wavelength at 450 nm. The determination of quinine in tonic water samples is carried out according to the following procedure [16]: 1 mL of tonic water (previously degassed by 15 min sonication in an ultrasonic bath) was pipetted into a 100 mL volumetric flask and dilute to the mark with 0.05 M sulfuric acid. The fluorescence intensity of this solution is measured in a fluorescence spectrometer in 10 mm pathway quartz cells at 350 nm excitation wavelength and at 450 nm emission wavelength. The quinine concentration is interpolated in the corresponding calibration curve. All analytical operations were done at 20 ± 4°C.

The specification equation for estimating the quinine concentration (mg/L) in tonic water samples is given by

$$Z = \frac{C_{cal} V}{V_0 R} f_{prec} \tag{15}$$

where C_{cal} is the value (mg/L of quinine) interpolated in the calibration curve from the measured fluorescence intensity of the assay, V is the volume of the assay (100 mL), V_0 is the sample volume (1 mL), R is the recovery of the assay and f_{prec} is the factor corresponding to the assay precision which has a value of 1, but an uncertainty equals to the precision standard deviation of the Z measurement. Recovery and precision data are taken from the in-house validation study of the method. The corresponding cause and effect Ishikawa diagram is depicted in **Figure 1**.

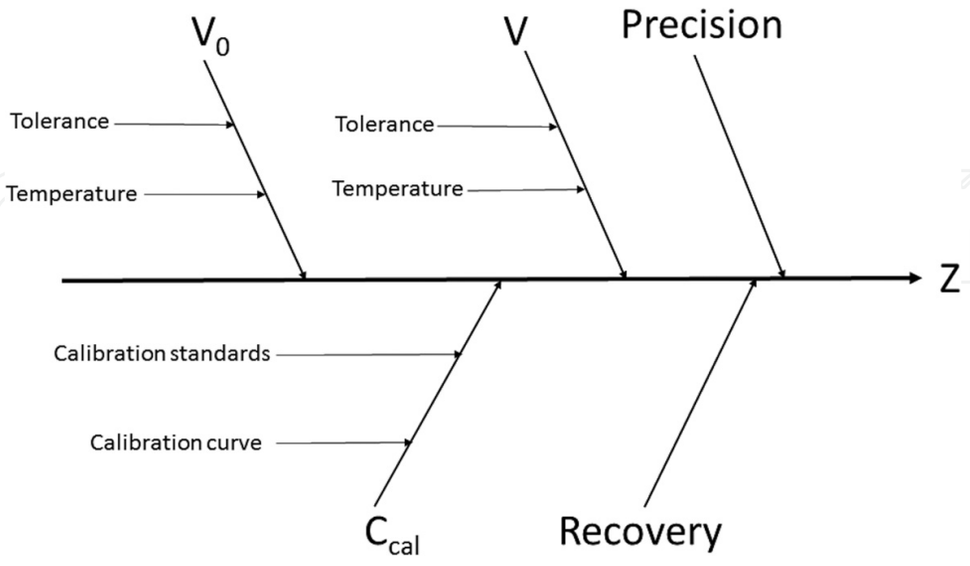

Figure 1. Cause and effect diagram for the fluorimetric determination of quinine in tonic water.

According to the fishbone plot, the uncertainty budget is as follows:

$$u_{rel}^2(Z) = u_{rel}^2(C_{cal}) + \sum_{i=1}^{5} u_{rel}^2(C_i) + u_{rel}^2(V) + u_{rel}^2(V_0) + u_{rel}^2(R) + RSD_{prec}^2 \quad (16)$$

Now, each uncertainty contribution is studied and evaluated.

2.1. Uncertainty coming from calibration and standards

In order to establish the corresponding calibration curve, a stock solution of quinine was prepared by weighing 121.6 mg of quinine sulfate dihydrate with a minimum purity of 99% (or 99.5 ± 0.5%) and dissolving and diluting 0.05 M sulfuric acid to 1000 ml in a volumetric flask. The concentration of this stock solution corresponds to 100 mg/L of quinine base.

Six working standards solution covering from 0.2 to 1.2 mg/L quinine were prepared by pipetting 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 mL of the stock solution and diluting with 0.05 M sulfuric acid in a 50 mL volumetric flask, leading to concentrations of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 mg/L quinine, respectively. The fluorescence intensity of each working standard at 350 nm excitation wavelength and at 450 nm emission wavelength was measured in triplicate. The results are shown in **Table 1**.

Fluorescence intensities show a linear behavior against the quinine concentration according to a calibration straight line with a correlation coefficient of about 0.999, and the following features:

$$b_1 = 784.76,\ \ b_0 = 13.67,\ \ s_{x/y} = 3.15,\ \ N = 18,\ \ \overline{C} = 0.7,\ \ \sum_{i=1}^{18} \left(C_i - \overline{C}\right)^2 = 2.1$$

The corresponding calibration uncertainty assuming that the analytical signal is measured in triplicate (m = 3) from Eq. (11) is given by:

Working standard solution, mg/L	**Fluorescence, AU**		
	Trial 1	**Trial 2**	**Trial 3**
0.2	171	172	171
0.4	327	328	330
0.6	484	481	481
0.8	642	640	643
1.0	800	798	799
1.2	954	958	955

Table 1. Fluorescence intensities (UA) for the five working standard solutions, measured in triplicate.

http://dx.doi.org/10.5772/intechopen.72048

$$u(C_{cal}) = 4 \times 10^{-3}\sqrt{\frac{1}{3}+\frac{1}{18}+\frac{(C_{cal}-0.7)^2}{2.1}} \tag{17}$$

Uncertainty due to preparation of working calibration standards is computed from Eq. (12). The uncertainty of the standard mass can be evaluated according to Eq. (7). In our case, the balance specifications were: Linearity (a_L): 0.2 mg. Sensitivity temperature coefficient (a_T): $2.5 \times 10^{-6}\,\mathrm{K}^{-1}$. The calibration certificate indicates an expanded uncertainty of 8×10^{-4} g with a coverage factor, k = 2. Because the analytical operations are performed at 20° ± 4°C and ΔT = 4°. Thus, we have:

$$u(m_{std}) = \sqrt{\frac{2}{3}(0.2)^2 + \frac{m_{std}^2\left(2.5 \times 10^{-6}\right)^2(4)^2}{9} + (0.4)^2}$$
$$= \sqrt{0.187 + 1.11 \times 10^{-11} m_{std}^2}; 0.432mg$$

The uncertainty of purity is evaluated from the specification: 0.995 ± 0.005 and assuming a rectangular distribution. Thus, $u(P) = \frac{0.005}{\sqrt{3}} = 2.9 \times 10^{-3}$. Uncertainty in volumes (from pipettes or volumetric flasks) are calculated from Eq. (8). The corresponding tolerances for glassware laboratory (Class A) are gathered in **Table 2**, except for the class A graduated pipette of 1 mL (for delivering volumes from 0.1 to 0.6 mL) which is ±0.006.

In the case of working standards, $V_i = 0.1, 0.2, 0.3, 0.4, 0.5$ and 0.6 mL for each working solution, $V_s = 1000\,\mathrm{mL}$ and $V_f = 50\,\mathrm{mL}$. Accordingly, we get

$$u(V_1) = \sqrt{\frac{(0.006)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 0.1^2(4)^2}{3}} = 2.45 \times 10^{-3}$$
$$u(V_2) = \sqrt{\frac{(0.006)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 0.2^2(4)^2}{3}} = 2.45 \times 10^{-3}$$
$$u(V_3) = \sqrt{\frac{(0.006)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 0.3^2(4)^2}{3}} = 2.46 \times 10^{-3}$$
$$u(V_4) = \sqrt{\frac{(0.006)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 0.4^2(4)^2}{3}} = 2.46 \times 10^{-3}$$
$$u(V_5) = \sqrt{\frac{(0.006)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 0.5^2(4)^2}{3}} = 2.46 \times 10^{-3}$$
$$u(V_6) = \sqrt{\frac{(0.006)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 0.6^2(4)^2}{3}} = 2.47 \times 10^{-3}$$
$$u(V_s) = \sqrt{\frac{(0.3)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 1000^2(4)^2}{3}} = 0.5$$
$$u(V_f) = \sqrt{\frac{(0.05)^2}{6}+\frac{\left(2.1 \times 10^{-4}\right)^2 50^2(4)^2}{3}} = 0.0317$$

Level	Theoretical concentration	Predicted concentration				
		Day 1	Day 2	Day 3	Day 4	Day 5
1	66	65.33	66.81	67.44	65.72	66.61
1	66	65.38	66.79	67.48	65.70	66.36
1	66	65.22	66.72	67.48	65.88	66.70
2	83	84.49	82.83	82.65	82.30	83.74
2	83	84.53	82.77	82.70	82.51	83.82
2	83	84.60	82.92	82.56	82.48	83.65
3	100	100.25	101.36	99.98	98.84	99.60
3	100	100.20	101.44	100.02	98.93	99.77
3	100	100.32	101.50	99.87	98.75	99.82

Table 2. Predicted concentration of the spiked placebos expressed in mg/L quinine.

The total relative uncertainty of the working standards can be evaluated by avoiding multiple counting as follows:

$$\begin{aligned} u_{rel}^2(C_i) &= \frac{u^2(m_{std})}{m_{std}^2} + \frac{u^2(P)}{P^2} + \sum_{i=1}^{6} \frac{u^2(V_i)}{V_i^2} + \frac{u^2(V_s)}{V_s^2} + \frac{u^2(V_f)}{V_f^2} \\ &= \frac{0.432^2}{121.6^2} + \frac{\left(2.9 \times 10^{-3}\right)^2}{0.995^2} + \frac{\left(2.45 \times 10^{-3}\right)^2}{0.1^2} + \frac{\left(2.45 \times 10^{-3}\right)^2}{0.2^2} \\ &\quad + \frac{\left(2.46 \times 10^{-3}\right)^2}{0.3^2} + \frac{\left(2.46 \times 10^{-3}\right)^2}{0.4^2} + \frac{\left(2.47 \times 10^{-3}\right)^2}{0.5^2} \frac{\left(2.47 \times 10^{-3}\right)^2}{0.6^2} \\ &\quad + \frac{0.5^2}{1000^2} + \frac{0.0317^2}{50^2} \\ &= 9.18 \times 10^{-4} \end{aligned} \tag{18}$$

2.2. Uncertainty of assay and sample volumes

The uncertainties of the assay and sample volume are also estimated from Eq. (8) and tolerances of **Table 2**:

$$\begin{aligned} u(V) &= \sqrt{\frac{(0.08)^2}{6} + \frac{\left(2.1 \times 10^{-4}\right)^2 (100)^2 (4)^2}{3}} = 0.058 \\ u_{rel}^2(V) &= \frac{0.058^2}{100^2} = 3.36 \times 10^{-7} \\ u(V_0) &= \sqrt{\frac{(0.006)^2}{6} + \frac{\left(2.1 \times 10^{-4}\right)^2 (1)^2 (4)^2}{3}} = 2.5 \times 10^{-3} \\ u_{rel}^2(V_0) &= \frac{\left(2.5 \times 10^{-3}\right)^2}{1^2} = 6.25 \times 10^{-6} \end{aligned} \tag{19}$$

2.3. Uncertainty of precision and trueness from in-house validation

The study of precision (intermediate precision) and trueness (recovery of assay) for the fluorimetric determination of quinine in tonic water was performed by using validation standards (spiked placebos) as indicated by González and Herrador [16]. Validation standards of quinine in tonic water matrix were prepared at low (66 mg/L), medium (83 mg/L) and high level (100 mg/L), covering the whole range of analyte concentrations (from 80 to 120% of 83 mg/L of quinine that is the recommended value of quinine in tonic waters by the FAD [17]). Both precision and trueness study was performed by predicting the actual concentrations of the three spiked placebos according to the recommended fluorimetric procedure for quinine determination. Measurements were made on 5 days for each validation standard with three replications of the assay. The results obtained are presented in **Table 3**.

The best way to estimate both the uncertainty contribution of intermediate precision and the recovery (or bias) of the analytical assay when validation standards are available, is using ANOVA at a given concentration of the validation standard, namely *T*, considering p different conditions (5 days in this case) and n replications (3 days in this case). From the ANOVA results (within conditions variance, S_W^2, between conditions variance, S_B^2, and total mean, $\overline{\overline{x}}$), the values of variance due to the condition (here, days), $S_{condition}^2$, the variance of repeatability, S_r^2, the variance of intermediate precision, S_{IP}^2 as well as the bias and recovery together with their uncertainties can be easily computed [14, 18]:

$$S_{condition}^2 = \frac{S_B^2 - S_W^2}{n};\;\; S_r^2 = S_W^2;\;\; S_{IP}^2 = S_r^2 + S_{condition}^2; RSD_{IP}^2 = \frac{S_{IP}^2}{\overline{\overline{x}}^2}$$
$$R = \frac{\overline{\overline{x}}}{T};\;\; u^2(R) = \frac{S_{IP}^2 - \frac{n-1}{n}S_r^2}{pT^2};\;\; u_{rel}^2(R) = \frac{S_{IP}^2 - \frac{n-1}{n}S_r^2}{p\overline{\overline{x}}^2} \tag{20}$$

Class A glassware.	Capacity, mL	Tolerance, mL
Burette	50	± 0.05
	25	± 0.03
	10	± 0.02
Pipette	40–50	±0.05
	15–30	±0.03
	8–10	±0.02
	3–7	± 0.01
	1–2	±0.006
Volumetric flask	1000	±0.3
	500	±0.15
	100	±0.08
	50	±0.05
	25	±0.03

Table 3. Tolerances for class A laboratory glassware.

Nominal concentration (T, mg/L quinine)	$\bar{\bar{x}}$	RSD^2_{IP}	R	$u^2_{rel}(R)$
66	66.38	1.65×10^{-4}	1.0057	3.28×10^{-5}
83	83.24	1.13×10^{-4}	1.0029	2.25×10^{-5}
100	100.04	8.87×10^{-5}	1.0004	1.77×10^{-5}

Table 4. Relative precision and uncertainty of recovery for the three validation standards in the fluorimetric determination of quinine in tonic water.

Thus, values of RSD^2_{IP} and $u^2_{rel}(R)$ are obtained for each spiked placebo. These data are presented in **Table 4**. A significance test has been used to evaluate if the recovery is significantly different from unity for each spiked placebo:

$$t = \frac{|1 - R|}{u(R)}$$

This value is then compared with the two-tailed critical value of tabulated Student-t statistic for np-1 degrees of freedom (14 in our case) at a 95% confidence level ($t_{crit}(14, 95\%) = 2.145$). For the three studied validation standards, recoveries were significantly equal to unity, and we can set $R = 1$ in all cases.

As can be seen in Eq. (20), the value of RSD^2_{IP} contains $u^2_{rel}(R)$ and accordingly, as it was indicated above, we can neglect the contribution $u^2_{rel}(R)$ in the uncertainty budget. The value of relative precision for the determined quinine concentration is taken as $RSD^2_{prec} = \frac{RSD^2_{IP}}{m}$ (here, m = 3).

Now, all contributions of specification factors have been included in the budget. Consider now that a sample of tonic water (Schweppes) has been analyzed by following the recommended procedure. The response is measured in triplicate (m = 3), leading to a fluorescence intensity (AU) of 617.5, 618.1 and 616.7. The mean value is $Y_0 = 617.43$ that corresponds to a quinine concentration of the assay of $C_{cal} = \frac{617.43 - 13.67}{784.76} = 0.76936$. Accordingly, the value of calibration uncertainty from Eq. (17), but neglecting the radical term 1/3 in order to avoid double counting, gives $u(C_{cal}) = 10^{-3}$ and $u^2_{rel}(C_{cal}) = 1.7 \times 10^{-6}$. The concentration of quinine in the sample according Eq. (15) with $R = 1$ and $f_{prec} = 1$ is Z = 76.936 ppm. We can interpolate this value in **Table 4** in order to estimate the corresponding $RSD^2_{IP} = 1.31 \times 10^{-4}$ that leads to $RSD^2_{prec} = \frac{1.31 \times 10^{-4}}{3} = 4.38 \times 10^{-5}$. Then, by applying Eq. (16), disregarding the recovery contribution, we get

$$\begin{aligned} u^2_{rel}(Z) &= u^2_{rel}(C_{cal}) + u^2_{rel}(C_i) + u^2_{rel}(V) + u^2_{rel}(V_0) + RSD^2_{prec} \\ &= 1.7 \times 10^{-6} + 9.18 \times 10^{-4} + 3.37 \times 10^{-7} + 6.25 \times 10^{-6} + 4.38 \times 10^{-5} \\ &= 0.00097 \end{aligned}$$

Thus, $u_{rel}(Z) = 0.03115$ and $u(Z) = 76.936 \times 0.03115 = 2.396$. By assuming a Gaussian coverage factor of 95% confidence k = 2, the expanded uncertainty is $U(Z) = 4.792$ and the quinine concentration of Schweppes tonic water sample is $Z = 77 \pm 5 ppm$.

3. Selected applications in tabular form

A more detailed picture of most recent selected papers about the "Guide to the Expression of Uncertainty in Measurement" is depicted in **Table 5**, giving an idea of the importance and

Content	Authors	Ref.
General overview about concepts, models, methods, and computations that are commonly used for the evaluation of measurement uncertainty, and their application in realistic examples drawn from multiple areas of science and technology.	Possolo and Iyer, 2017	[19]
A complete procedure to encompass an uncorrected bias into the expanded uncertainty with a fixed coverage probability.	Synek, 2017	[20]
Reported scientific uncertainties by analyzing 41,000 measurements of 3200 quantities from medicine, nuclear and particle physics, and interlaboratory comparisons ranging from chemistry to toxicology.	Bailey, 2016	[21]
The GUM revision: the Bayesian view toward the expression of measurement uncertainty.	Lira, 2016	[22]
Comparing methods for evaluating measurement uncertainty given in the Joint Committee for Guides in Metrology 'Evaluation of Measurement Data' documents.	Stant et al., 2016	[23]
In pursuit of a fit-for-purpose uncertainty guide: the move away from a frequentist treatment of measurement error to a Bayesian treatment of states of knowledge is misguided.	White, 2016	[24]
Three controversies faced in the development of GUM document: (i) the acceptance of the existence of 'true values', (ii) the association of variances with systematic influences and (iii) the representation of fixed but unknown quantities by probability distributions.	Willink, 2016	[25]
A new way to express uncertainty of measurement is proposed that allows for the fact that the distribution of values attributed to the measurand is sometimes approximately lognormal and therefore asymmetric around the measurement value.	Ramsey and Ellison, 2015	[26]
Revision of the GUM: reasons why the Guide needed a revision, and why that revision could not go in a direction different from the one that it has been taken.	Bich, 2014	[27]
Validating the applicability of the GUM procedure.	Cox and Harris, 2014	[28]
Evolution in thinking and its impact on the terminology that accompanied the development of the GUM	Ehrlich, 2014	[29]
The developments in uncertainty concepts and practices that led to the third edition of the Eurachem Guide on uncertainty evaluation.	Ellison, 2014	[30]
A review of monte carlo simulation using microsoft excel for the calculation of uncertainties through functional relationships, including uncertainties in empirically derived constants.	Farrance and Frenkel, 2014	[31]
Evaluation of mass measurements in accordance with the GUM. The importance of reporting calibration results in a compact way that is easily propagated down the traceability chain is also discussed.	Nielsen, 2014	[32]
Overview about statistical models and computation to evaluate measurement uncertainty.	Possolo, 2014	[33]
Discussion about recent situation in measurement science, and how to obtain a reliable measurement result using the expression of metrological traceability together with measurement uncertainty.	Imai,2013	[34]
A new strategy for the analytical validation based on the uncertainty profile as a graphical decision-making tool, and to exemplify a novel method to estimate the measurement uncertainty.	Saffaj et al., 2013	[35]

Content	Authors	Ref.
Monte Carlo approach for estimating measurement uncertainty using standard spreadsheet software.	Chew et al., 2012	[36]
General overview of the GUM and to show how the calculation of uncertainty in the measurand may be achieved through a functional relationship.	Farrance and Frenkel, 2012	[37]
Estimation of the measurement uncertainty in quantitative determination of ketamine and norketamine in urine using a one-point calibration method.	Ma et al., 2012	[38]
EURACHEM/CITAC workshop on recent developments in measurement uncertainty. Contains a selection of the contributed papers at this workshop and show how the evaluation of uncertainty is now being applied to a wide range of analyses.	Williams, 2012	[39]
Highlight some of the differences between the two concepts of total error and uncertainty but also to stress their main similarities.	Rozet et al., 2011	[40]
The assurance as a result of blood chemical analysis by ISO-GUM and Quality Engineering.	Iwaki, 2010	[41]
Managing quality vs. measuring uncertainty in the medical laboratory. The paper argues that total error provides a practical top-down estimate of measurement uncertainty in the laboratory, and that the ISO/GUM model should be primarily directed to and applied by manufacturers.	Westward, 2010	[42]
Comparison of the approach to measure uncertainties proposed in ISO 5725 and GUM from a statistician point of view.	Deldossi and Zappa, 2009	[43]
Utilizing the correlations between the N individual results, an equation is derived to combine the N individual uncertainties of N measurements. Using the newly derived equation including the correlation coefficient, three measurement uncertainties of three measurement results are combined as an example.	Nam et al., 2009	[44]
From GUM to alternative methods for measurement uncertainty evaluation.	Priel, 2009	[45]
Critical debate about the revision of the Guide to the expression of uncertainty in measurement.	Bich, 2008	[46]
Course aimed at developing understanding of measurement and uncertainty in the introductory physics laboratory. The course materials, in the form of a student workbook, are based on the probabilistic framework for measurement as recommended by the International Organization for Standardization in their publication GUM.	Buffler et al., 2008	[47]
Scientific discussion about measurement uncertainty and chemical analysis.	Kadis, 2008	[48]
Treatment of uncorrected measurement bias in uncertainty estimation for chemical measurements.	Magnusson and Ellison, 2008	[49]
A critical overview of the current doubtful practice on presentation of correlated data in the physics literature and in the scientific and technological databases.	Ezhela, 2007	[50]
A detailed step-by-step guide to analytical method validation, considering the most relevant procedures for checking the quality parameters of analytical methods.	González and Herrador, 2007	[9]
Development of the concept of uncertainty in measurement and the methods for its quantification from the classical error analysis to the modern approaches based on the GUM.	Kacher et al., 2007	[51]
Measurement uncertainty: top-down and bottom-up approach, tools for its determination uncertainty sources and practical examples.	Meyer, 2007	[52]
Critical review about calibration-, uncertainty-, and recovery-related documents from 10 consensus-based organizations.	Vanatta and Coleman, 2007	[53]
Evolution of the GUM: documents relating to the GUM planned by Joint Committee for Guides in Metrology.	Bich et al., 2006	[54]

Content	Authors	Ref.
Calculating uncertainty of measurement for serology assays by use of precision and bias.	Dimech et al., 2006	[55]
Comparison of ISO-GUM, draft GUM Supplement 1 and Bayesian statistics using simple linear calibration.	Kacher et al., 2006	[56]
Estimation of the measurement uncertainty of analytical assays based on the LGC/VAM protocol from validation data in the light of the study of precision, trueness and robustness.	González et al., 2005	[57]
Philosophy behind the GUM, and demonstrates, with a medical physics measurement example of how the GUM recommends uncertainties be calculated and reported.	Gregory et al., 2005	[58]
The limitations of the GUM for evaluating the uncertainty of indirect measurements. The propagation of distributions as the best way to evaluate the measurement. Uncertainty and the use of Monte-Carlo method for performing the propagation of distributions is outlined and discussed.	Herrador et al., 2005	[59]
Comparison of six commercial programs devoted to the estimation of measurement uncertainty for feasibility in order to be applied in routine chemical analysis.	Jurado and Alcázar, 2005	[60]
Treatment of bias in estimating measurement uncertainty.	O'Donnell and Hibbert, 2005	[61]
Statistical analysis of Consultative Committees of the International Committee of Weights and Measures (CIPM) key comparisons based on the ISO Guide.	Kacker et al., 2004	[62]
General overview of the uncertainty of measurement concept, with minimal metrological terminology, and also practical guidelines to assist pathology laboratories comply with this accreditation requirement.	White and Farrance, 2004	[63]
Approach to determine the overall uncertainty by combining the uncertainties of the individual results when the difference is statistically significant by GUM.	Choi et al., 2003	[64]
An appraisal on the guide to expression of uncertainty in measurement approach for estimating uncertainty.	Kristiansen, 2003	[65]
Critique of the Guide to the expression of uncertainty in measurement method of estimating and reporting uncertainty in diagnostic assays.	Krouwer, 2003	[66]
Effect of non-significant proportional bias in the final measurement uncertainty.	Maroto et al., 2003	[67]
Background of the GUM. The knowledge of the respective measurement and other fundamental aspects which have been included in the EA-4/02 requirements document published by the European co-operation for accreditation.	Kessel, 2002	[68]
Operational definitions of uncertainty taking into account the differences in the ways in which truth, uncertainty and error are conceived.	Hund et al., 2001	[69]
Approaches to the evaluation of uncertainties associated with recovery	Barwick and Ellison, 1999	[70]
Review of the concepts and practices of data quality in analytical chemistry in relation to uncertainty. It is addressed primarily to the bodies that will be responsible for the introduction of uncertainty into routine practice.	AMC, 1995	[71]
Future trends in analytical quality assurance, the evaluation of the quality of analytical results by estimation of their uncertainties. The present state-of-the-art is described, and the impact caused by the declaration of uncertainties in chemical results is foreseen.	Cortez, 1995	[72]
Critical reflexion about the uncertainty concept and its method for estimation.	Thompson, 1995	[73]
Guidelines for evaluating and expressing the uncertainty of NIST measurement results.	Taylor and Kuyatt, 1994	[74]

Table 5. Selected papers about the "Guide to the Expression of Uncertainty in Measurement (GUM)".

relevance of the topic in different fields. Emphasis is stressed on reviews and taking into account the high number of references available, the authors apologize for those they may have overlooked or inadvertently omitted. Selected applications about the estimation of uncertainty in volumetric glassware, analytical balance and calibration curves, as well as the evaluation of the measurement uncertainty in classical and instrumental techniques are shown in **Tables 6** and **7**. **Figure 2** shows the number of publications cited per year, whereas in **Figure 3**, the number of paper cited by journal for the most cited journals appears.

Content	Reference	Ref.
Volumetric glassware		
Uncertainty on using graduated volumetric glassware for the concentration of samples (concentration tube) and its effect on measurement accuracy.	Matsuda et al., 2015	[75]
Experimental study on evaluation of uncertainty in volumetric measurement: pipettes, graduated pipettes, graduated burettes, volumetric flasks and micropipettes used in various analytical and biological studies.	Mukund et al., 2015	[76]
Influencing factors in uncertainty measurement that affect mass and volume determination. Technical specification of an analytical balance such as: readability, repeatability, linearity, off-center loading and hysteresis and for volumetric glassware: repeatability, readability, temperature coefficient of sensitivity, temperature scattering, meniscus reading and environmental conditions (temperature and humidity) are considered.	Rahman et al., 2015	[77]
Analysis of the results obtained in the calibration of electronic analytical balances.	Valcu and Baicu, 2012	[78]
Influence quantities for the uncertainty of a volumetric operation with glass instruments: Calibration, handling repeatability, and the maximum permissible error.	Meyer et al., 2010	[79]
Comparison of two different approaches in the uncertainty calculation of gravimetric volume calibration: mainstream GUM and Monte Carlo method.	Batista et al., 2009	[80]
Ranking of the contributions to the uncertainty of titrimetric results.	Wampfler and Rösslein, 2009	[81]
Volume calibration of 1000 μl micropipettes. Inter-laboratory comparison between six national metrology institutes.	Batista et al., 2008	[82]
Primer on weighing uncertainties in radionuclidic metrology.	Collé, 2008	[83]
Measurement and uncertainty evaluation of nanofluid particle concentration using volumetric flask method.	Kostic et al., 2006	[84]
Detailed analysis of relevant uncertainty sources with two different procedures for evaluating the uncertainty identified: one of them relies on the prescribed tolerance while the other is based on the experimental estimation of the actual performance in the user's hand. The uncertainty budget for each of these two approaches is evaluated, analyzed and illustrated with a numerical example.	Kadis, 2004	[85]
Sources for both the gravimetric and spectrophotometric pipette calibration methods.	Clark and Shull, 2003	[86]
Sampling variance of ultra-dilute solutions.	Efstathiou, 2000	[87]
Experimental study using gravimetry in order to measure the variances observed in aliquot volumes delivered by graduated burettes operating with various flow-rates and surface tensions and with the burette tip immersed and not immersed in the receiving liquid.	Schwartz, 1990	[88]
Statistical methodology required for rigorous calibration of devices that are designed to deliver a fixed aliquot volume without having to read volume graduations lines.	Schwartz, 1989	[89]

Content	Reference	Ref.
Minimizing relative error in the preparation of standard solutions by judicious choice of volumetric glassware.	Lam and Isenhour, 1980	[90]
Practical guide to estimates of uncertainty of the calibration of balances.	Anonymous	[91]
Analytical balance		
Calculating measurement uncertainty of the "conventional value of the result of weighing in air".	Flicker and Tran, 2016	[92]
Weighing uncertainties in quantitative source preparation for radionuclide metrology.	Lourenço and Bobin, 2015	[93]
Influencing factors in uncertainty measurement that affect mass and volume determination. Technical specification of an analytical balance: readability, repeatability, linearity, off-center loading and hysteresis and for volumetric glassware: repeatability, readability, temperature coefficient of sensitivity, temperature scattering, meniscus reading and environmental conditions (temperature and humidity).	Rahman et al., 2015	[77]
Procedure for evaluating the uncertainty of mass measurements when using electronic balances based on the internal quality-control routine, the calibration process, the specification data sheet, and the considered weighing scenario.	González and Herrador, 2007	[9]
Influence factors that affect in uncertainty measurement of a mass determination. Technical specifications of a balance: Readability, repeatability, non-linearity, sensitivity tolerance, temperature coefficient of sensitivity and effects of environmental factors such as: air humidity, air pressure and air buoyancy.	Salahinejad and Aflaki, 2007	[94]
The influence of atmospheric pressure, air temperature, and relative air humidity on weighing results was determined in a long-term experiment.	Pozivil et al., 2006	[95]
The uncertainty evaluation of mass measurements when using "in-house" calibrated analytical balances is revisited according to the GUM.	González et al., 2005	[96]
Good practice guide is intended as a useful reference for those involved in the practical measurement of mass and weight.	Davidson et al., 2004	[97]
Influence factors which are part of the combined measurement uncertainty of a mass determination and their interplay, namely the technical specifications of the balance (repeatability, nonlinearity, sensitivity tolerance, and temperature coefficient of the sensitivity) and the effect of air buoyancy.	Reichmuth et al., 2004	[98]
A new method to correct for the largest systematic influence in mass determination – air buoyancy. Full description of the most relevant influence parameters and the combined measurement uncertainty is evaluated according to the ISO–GUM approach.	Wunderli et al., 2003	[99]
Evaluation of methods for estimating the uncertainty of electronic balance measurements. Terminology used to describe measurement quality, i.e., "accuracy," "precision," "linearity," "hysteresis," "measurement uncertainty" (MU), and the various contributors to MU, and will discuss the advantages and limitations of various methods for estimating MU.	Clark and Shull, 2001	[100]
The influence of variations in atmospheric pressure on the uncertainty budget of weighing results.	Kehl et al., 2000	[101]
Comprehensive mass metrology: A survey of the current problems surrounding mass determination that is comprehensive but does not purport to be complete.	Kochsiek and Gläser, 2000	[102]
Calibration curve		
Common mistakes in evaluating the uncertainty when pursuing that strategy, as revealed in current chromatographic literature.	Kadis, 2017	[13]

Content	Reference	Ref.
The quality coefficient as performance assessment parameter of straight line calibration curves in relationship with the number of calibration points.	de Beer et al., 2012	[103]
Comparison in the evaluation of measurement uncertainty in analytical chemistry testing between the use of quality control data and a regression analysis.	Sousa et al., 2012	[104]
Application of various methodologies concerning the estimation of the standard uncertainty of a calibration curve used for the determination of sulfur mass concentration in fuels.	Theodorou et al., 2012	[105]
The evaluation of uncertainty for linear calibration curves generation in analytical laboratories.	Nezhikhovskiy et al., 2006	[106]
Uncertainty functions: a way of summarizing or specifying the behavior of analytical systems.	Thompson, 2011	[107]
Calibration in atomic spectrometry: a tutorial review dealing with quality criteria, weighting procedures and possible curvatures.	Mermer, 2010	[108]
Critical review on the usual procedures for testing the accuracy of analytical methods.	Kemény et al., 2009	[109]
Three different techniques for fitting straight lines to experimental data and evaluation of uncertainty: (i) traditional fitting by least-squares, (ii) a Bayesian linear-regression analysis and (iii) an analysis according to the propagation of probability density functions attributed to the points measured.	Willink, 2008	[110]
New method for propagating uncertainty, based on interpolation theory, to solve the problem in linear interpolating equations. The method is extended to nonlinear equations, and to over-determined linear or nonlinear equations fitted by least-squares methods.	White and Saunders, 2007	[111]
Propous theory to calculate the confidence intervals of calibration lines in the above situations. Analyses made up of sample weighing, dilution, High Performance Liquid Chromatography measurement and calibration with the linear least-squares fitting are taken as examples.	Hayashi and Matsuda, 2006	[112]
Commonly used expression for the standard error of a result obtained from a straight line calibration is extended to a quadratic calibration, and the case where weighted regression is necessary.	Hibbert, 2006	[113]
The use of Crystal-Ball is illustrated with two working examples dealing with specification models of non-linear features and with correlated variables (such as the slope and intercept of calibration straight lines).	González et al., 2005	[114–115]
Introduction of a novel approach on actual calibration data for the determination of Pb by inductively coupled plasma-atomic emission spectroscopy. The improved calibration uncertainty was verified from independent measurements of the same sample by demonstrating statistical control of analytical results and the absence of bias.	Heydorn and Anglov, 2002	[116]
Evaluation of measurement uncertainty for analytical procedures using a linear calibration function: the uncertainty deduced from repeated observations of the sample vs. the uncertainty deduced from the standard residual deviation of the regression.	Brüggemann and Wennrich, 2002	[117]
Evaluation of the most conflicting points concerning linear regression. Confidence bands and a discussion about the use of a line through the origin are also included. In addition, the simplest expressions for expressing parameters to the appropriate significant figures from built-in calculator programs are also provided.	Giordano, 1999	[118]

Content	Reference	Ref.
Strategy for the validation of the calibration procedure in atomic absorption spectrometry. In order to accomplish this, the suitability of different experimental designs and statistical tests, to trace outliers, to examine the behavior of the variance and to detect a lack-of-fit, was evaluated. Parametric as well as randomization tests were considered.	Penninckx et al., 1996	[119]
The "precision pattern space" is introduced in order to find the general expression for the law of random error propagation. A new approach to the determination of the optimum working range in spectrophotometric procedures has been developed. The method involves the use of the calibration curve and the application of the Laplacian operator to concentration.	Asuero et al., 1988	[120]

Table 6. Selected papers about the estimation of uncertainty in volumetric glassware, analytical balance and calibration curves.

Content	Reference	Ref.
Gravimetry		
Evaluation of purity with its uncertainty value in high purity lead stick by conventional and electro-gravimetric methods.	Singh et al., 2013	[121]
The determination of barium by the gravimetric method, in which the precipitation of $BaSO_4$ was formed and weighed, coupled with instrumental measurement of trace constituents was studied. Sources of uncertainty were assessed thoroughly.	Li et al., 2002	[122]
Titrimetry		
Measurement procedure for precisely determining hypochlorite in commercial bleaches, with established traceability and full description of its uncertainty using automatic potentiometric titration.	Barbieri Gonzaga and Rodrigues Cordeiro, 2014	[123]
Calculation of measurement uncertainty in the determination of the concentration of a freshly prepared solution of sodium hydroxide using potassium hydrogen phthalate as the primary standard.	Mettler Toledo, 2014	[124]
Evaluation of measurement uncertainty components associated with the results of complexometric determination of calcium in ceramic raw materials using EDTA.	Basak and Kundu, 2013	[125]
Target measurement uncertainty as a tool for validation of uncertainties estimated by different approaches: determination of total hardness in drinking and natural waters.	Calisto et al., 2013	[126]
An easy uncertainty evaluation of the chemical oxygen demand titrimetric analysis in correlation with quality control and validation data.	Amanatidou et al., 2012	[127]
Uncertainty estimation in measurement of pKa values in nonaqueous media: a case study on basicity scale in acetonitrile medium.	Sooväli et al., 2006	[128]
Uncertainty of chemical oxygen demand determination in wastewater samples. The major sources of uncertainty of the result of measurement were identified as the purity of reagents, volumetric operations, gravimetric operations, bias, and the repeatability of the method.	Drolc et al., 2003	[129]
Analytical procedure for the determination of the concentration of hydrochloric acid by titration against a standardized sodium hydroxide solution. The expanded uncertainty of the final result is expressed, endeavoring, in particular	Pueyo and Vilalta, 1996	[130]

Content	Reference	Ref.
to evaluate covariances and to take into account the chemical behavior of the specific reagent.		
Potentiometry: Ion Selective Electrode		
Uncertainty evaluation in the chloroquine phosphate potentiometric titration: Application of three different approaches: The famous error-budget approach, the analytical method committee top-down and the last method chosen was the one proposed by Barwick and Ellison.	Rodomonte et al., 2006	[131]
Procedure to estimate the uncertainty of measurement applied to the fluoride determination of waters and wastewaters matrices by selective electrode potentiometry based on Eurachem Guide. The major sources of uncertainty were identified as the calibration standard solutions, fluoride concentration obtained by potential interpolation of the regression line and the precision.	Sousa and Trancoso, 2005	[132]
Estimation of uncertainty in measurement of the pK_a of a weak acid by potentiometric titration. The procedure is based on the ISO GUM.	Koort et al., 2004	[133]
Amperometry		
Tutorial review on measurement uncertainty estimation in amperometric sensors.	Helm et al., 2010	[134]
Electron probe microanalysis		
Case study of ISO GUM-based estimation of measurement uncertainty of quantitative surface elemental analysis by electron probe microanalysis.	Virro et al., 2008	[135]
Ultraviolet Spectrophotometry		
Procedure to estimate measurement uncertainty of a validated UV spectrophotometric method for quantification of desloratadine in tablet formulation.	Takano et al., 2017	[136]
Uncertainty in spectrophotometric analysis – "Error propagation break up", a novel statistical method for uncertainty management. For the assessment of the computations, different approaches are discussed, such as the contribution to the Combined Standard Uncertainty of the reproducibility, the repeatability, the total bias, the calibration curve, and the type of the measurand.	Amanatidou et al., 2011	[137]
Eevaluation of the uncertainty and metrological reliability of material concentration measurement considering sample preparation and chemical–physical transformation of spectrometric analysis.	Dobiliene et al., 2010	[138]
Uncertainty in modern spectrophotometers: An up-to-date view of UV–vis molecular absorption instruments and measurements.	Galbán et al., 2007	[139]
Overview of the most important uncertainty sources that affect analytical UV–Vis spectrophotometric measurements. Altogether, eight uncertainty sources are discussed that are expected to have influence in chemical analysis.	Sooväli et al., 2006	[128]
Procedure for estimation of measurement uncertainty of photometric analyis based on the ISO GUM method. Two variations of the procedure, for the calibration graph and the standard addition method, are discussed.	Traks et al., 2005	[140]
Evaluation of the uncertainty of measurement in the determination of manganese by spectrophotometric analysis. The standard uncertainty is evaluated for each input quantity. These are then appropriately combined to get the combined uncertainty of measurement.	Ramachandran and Rashmi, 1999	[141]
X-Ray Fluorescence Spectrometry		
Evaluation of uncertainty in the energy dispersive X-ray fluorescence determination of platinum in alumina.	Remya Devi et al., 2015	[142]

Content	Reference	Ref.
Uncertainty measurement evaluation of wavelength dispersive and energy dispersive X-ray fluorescence techniques for the Si and Utotal determination in U_3Si_2 nuclear fuel.	Scapin et al., 2011	[143]
Uncertainty calculations for the measurement of in vivo bone lead by X-ray fluorescence	O'Meara and Fleming, 2009	[144]
Effect of the sample matrix on measurement uncertainty in X-ray fluorescence analysis.	Morgenstern et al., 2005	[145]
Atomic Absorption Spectrometry		
Determination and uncertainty analysis of inorganic arsenic in husked rice by solid phase extraction and atomic absorption spectrometry with hydride generation.	Saxena et al., 2017	[146]
Optimization and measurement uncertainty estimation of hydride generation–cryogenic trapping–gas chromatography–cold vapor atomic fluorescence spectrometry for the determination of methylmercury in seawater.	Živković et al., 2017	[147]
Approach for the estimate of the uncertainty in measurement considering the individual sources related to the different steps of the method under evaluation as well as the uncertainties estimated from the validation data for the determination of mercury in seafood by using thermal decomposition/amalgamation atomic absorption spectrometry.	Torres et al., 2015	[148]
Methodology of evaluating the uncertainty of measurement of chemical composition using atomic absorption spectrometry.	Mahajan et al., 2012	[149]
Comparison of ISO-GUM and Monte Carlo methods for the evaluation of measurement uncertainty: Application to direct cadmium measurement in water by graphite furnace atomic absorption spectrometry.	Theodorou et al., 2011	[150]
Evaluation of measurement uncertainties for the determination of total metal content in soils by atomic absorption spectrometry.	Alves et al., 2009	[151]
Uncertainty statement of a mercury speciation analytical method using the relationships fixed by GUM (Guide to the Expression of Uncertainty in Measurement).	Jokai and Fodor, 2009	[152]
UV–Vis spectrophotometric and flame atomic absorption spectrometric analysis for iron determination in a pharmaceutical product were compared in terms of uncertainty budgets.	Jürgens et al., 2007	[153]
How to validate the calibration function is dealt with in detail using as an example based on measurements obtained for nickel determination by flame atomic absorption spectrometry. Assessing uncertainties related to linear calibration curves is also discussed.	Chui, 2007	[154]
Three approaches are compared for the evaluation of the combined uncertainty in the determination of mercury in aquatic sediments by an aqua regia extraction procedure.	Guevara-Riba et al., 2006	[155]
Full validation of a cold vapor atomic absorption spectrometry method for mercury determination in fishery products.	Haouet et al., 2006	[156]
Uncertainty of atomic absorption spectrometer.	Hirano et al., 2005	[157]
Estimate of uncertainty of measurement from a single-laboratory validation study: application to the determination of lead in blood.	Patriarca et al., 2004	[158]
Total uncertainty budget calculation for the determination of mercury in incineration ash (BCR 176R) by atomic fluorescence spectrometry.	Tirez et al., 2002	[159]

Content	Reference	Ref.
Uncertainty of measurement of the analysis of lead in blood by graphite furnace atomic absorption spectrometry calibrating with a commercial available standard.	O 'Donnell, 2000	[160]
The major sources of uncertainty of a method for determination of Pb in whole blood by atomic absorption spectrometry. The combined uncertainty was compared to the experimentally determined variation and a satisfactory agreement was found, indicating that no significant sources of uncertainty have been overlooked and that the method is in a state of statistical control.	Kristiansen et al., 1996	[161]
Nuclear Magnetic Resonance Spectroscopy		
Uncertainty budget for the results of measurements of purity of the agrochemical glyphosate using ^{1}H and ^{31}P quantitative nuclear magnetic resonance spectroscopy. The budget combines intralaboratory precision from repeated independent measurements of a batch, and other Type A and Type B effects.	Al-Deen et al., 2004	[162]
Inductively Coupled Plasma		
Results of prominent technologies of inductively coupled plasma mass spectrometry, for determination of chloride-isotope ratios ($^{35}Cl/^{37}Cl$) and inductively coupled plasma optical emission spectrometry for determination of sodium, were evaluated in terms of the true level of uncertainty and revealed a genuine problem for science that was not addressed in VIM3 and QUAM.	Andersen et al., 2016	[163]
Application of the GUM approach to estimate the measurement results uncertainty for the quantitative determination of Al, Ba, Fe, Mg, Mn, Pb, Sr. and Zn from document paper samples using Inductively Coupled Plasma Mass Spectrometer. The measurement uncertainty estimation was done based on identifying, quantifying and combining all the associated sources of uncertainty separately.	Tanase et al., 2015	[164]
Development, validation, and evaluation of measurement uncertainty of a method for quantitative determination of essential and nonessential elements in medicinal plants and their aqueous extracts by using inductively coupled plasma optical emission spectrometry.	Senila et al., 2014	[165]
Uncertainty budget for multi-elemental analysis of plant nutrients in conifer foliar material using inductively coupled plasma atomic emission spectrometry.	Ohlsson, 2012	[166]
Method for simultaneous inductively coupled plasma mass spectrometer determination of 13 elements in three types of honey from Poland. The method was validated, and the uncertainty budget was set up.	Chudzinska et al., 2012	[167]
Evaluation of the combined measurement uncertainty in isotope dilution by a multi-collector inductively coupled plasma mass spectrometer and the use of high-purity reference materials.	Fortunato and Wunderli, 2003	[168]
Validation of the determination of lead in whole blood by inductively coupled plasma mass spectrometer. Uncertainty of the centroid of the calibration graph was preferred to the evaluation of the linearity with ANOVA to validate the calibration procedure.	Bonnefoy et al., 2002	[169]
The measurement uncertainty associated with the determination of Ni in aqueous samples by inductively coupled plasma mass spectrometer has been calculated using a cause-and-effect approach. A cause-and-effect diagram was constructed to aid in the identification of the sources of uncertainty associated with the method.	Barwick et al., 1999	[170]

Content	Reference	Ref.
Mass spectrometry		
The application of the GUM to calculate standard uncertainties for routine uranium isotope mass spectrometry measurements for nuclear safeguards and nuclear metrology.	Bürguer et al., 2010	[171]
Chromatography		
Study to estimate a reasonable uncertainty for the measurement of the identified measurand, which is the mass concentration of ethanol, methanol, acetone, and isopropanol determined through dual capillary column headspace gas chromatograph (GC): GC calibration adjustment slope, GC analytical, and certified reference material.	Hwang et al., 2017	[172]
Development, validation and different approaches for the measurement uncertainty of a multi-class veterinary drugs residues liquid chromatography-mass spectrometry method for feeds.	Valese et al., 2017	[173]
Critical challenges regarding the validation of a quantitative multi-residue method for pharmaceuticals in wastewater making use of modern solid phase extraction-liquid chromatography-orbitrap high-resolution mass spectrometry. Particular attention is given to study in detail response linearity, to realistically estimate detection limits, and to express the measurement precision of the analyte concentration, obtained by external calibration.	Vergeynst et al., 2017	[174]
Validation and uncertainties evaluation of an isotope dilution-solid phase extraction-liquid chromatography–tandem mass spectrometry for the quantification of drug residues in surface waters.	Brieudes et al., 2016	[175]
Rapid determination of residues of pesticides in honey by gas chromatography–electron capture detector and gas chromatography–tandem mass spectrometry: Method validation and estimation of measurement uncertainty according to document No. SANCO/12571/2013.	Paoloni et al., 2016	[176]
A fast and simple liquid chromatography–tandem mass spectrometry method for detecting pyrrolizidine alkaloids in honey with full validation and measurement uncertainty.	Valese et al., 2016	[177]
Comparison of different methods to estimate the uncertainty in composition measurement by chromatography: two of them (guide to the expression of uncertainty in measurement method and prediction method) were compared with the Monte Carlo method.	Ariza et al., 2015	[178]
The role of uncertainty regarding the results of screening immunoassays in blood establishments.	Pereira et al., 2015	[179, 180]
Determination of polybrominated diphenyl ethers in water by a simple dispersive liquid–liquid microextraction–gas chromatography–mass spectrometry method. Validation parameters, including the calculation of the expanded uncertainty associated to the results in the range of quantification is included.	Santos et al., 2015	[181]
Establishing measurement of uncertainty for simultaneous bio-analytical determination of L-Carnitine and Metformin in human plasma by liquid chromatography–tandem mass spectrometry.	Terish Bino et al., 2015	[182]
Contribution of each stage in the developed procedure on the uncertainty measurement of the determination of volatile aromatic hydrocarbons in surface and underground water. The uncertainty sources were identified and illustrated in an effect diagram.	Pavlova et al., 2014	[183]

Content	Reference	Ref.
Evaluation of the sources of uncertainty in the determination of repaglinide in human plasma using liquid chromatography–tandem mass spectrometry.	Li et al., 2013	[184]
Measurement uncertainty of food carotenoid determination. The ISO guide was interpreted for analytical chemistry by EURACHEM. Measurement uncertainty was estimated based on laboratory validation data, including precision and method performance studies, and also, based on laboratory participation in proficiency tests.	Dias et al., 2012	[185]
Comparison of measurement uncertainty component estimations for three methods using the high-performance liquid chromatography techniques: determination of the type and content of aromatic hydrocarbons in diesel fuels and petroleum distillates by normal phase high-performance liquid chromatography, determination of nitrates in water samples by ion chromatography, and determination of molecular weights of polystyrene by size exclusion chromatography technique.	Tomić et al., 2012	[186]
The estimation and use of measurement uncertainty for a drug substance test procedure validated according to USP <1225>.	Weitzel, 2012	[187]
Estimation of the global uncertainty associated to the determination of pentachlorophenol in aqueous samples, by gas chromatography with mass spectrometric detection, after solid phase microextraction.	Brás et al., 2011	[188]
A high-performance technique that was originally developed for inductively coupled plasma optical emission spectrometry has been successfully translated to ion chromatography to enable analyses with extremely low uncertainty (0.2% Relative Expanded Uncertainty).	Brennan et al., 2011	[189]
Estimating the uncertainty related to GC-MS analysis of organo-chlorinated pesticides from water.	Pana et al., 2011	[190]
Development of a model system of uncertainty evaluations for multiple measurements by isotope dilution mass spectrometry: determination of folic acid in infant formula.	Kim et al., 2010	[191]
Basic terms, sources of uncertainty, and methods of calculating the combined uncertainty.	Konieczka and Namieśnik, 2010	[192]
Evaluation of uncertainty of measurement from method validation data: An application to the simultaneous determination of retinol and -tocopherol in human serum by high performance liquid chromatography.	Semeraro et al., 2009	[193]
Estimating the measurement uncertainty in forensic breath-alcohol analysis.	Gullberg, 2006	[194]
Uncertainty budget for final assay of a pharmaceutical product based on reverse phase high performance liquid chromatography.	Anglov et al., 2003	[195]
Analytical method to verify the accuracy of the natural abundance butyltin standard concentrations that are needed for their subsequent use in the reverse spike isotope dilution quantitation of enriched species-specific spikes. A full combined uncertainty calculation, accounting for all possible sources of uncertainty in the measurement process.	Yang et al., 2002	[196]
Propagation of uncertainty in high-performance liquid chromatography with UV–VIS detection.	Hibbert et al., 2001	[197]

Table 7. Selected papers on evaluation of the measurement uncertainty in classical and instrumental techniques.

http://dx.doi.org/10.5772/intechopen.72048

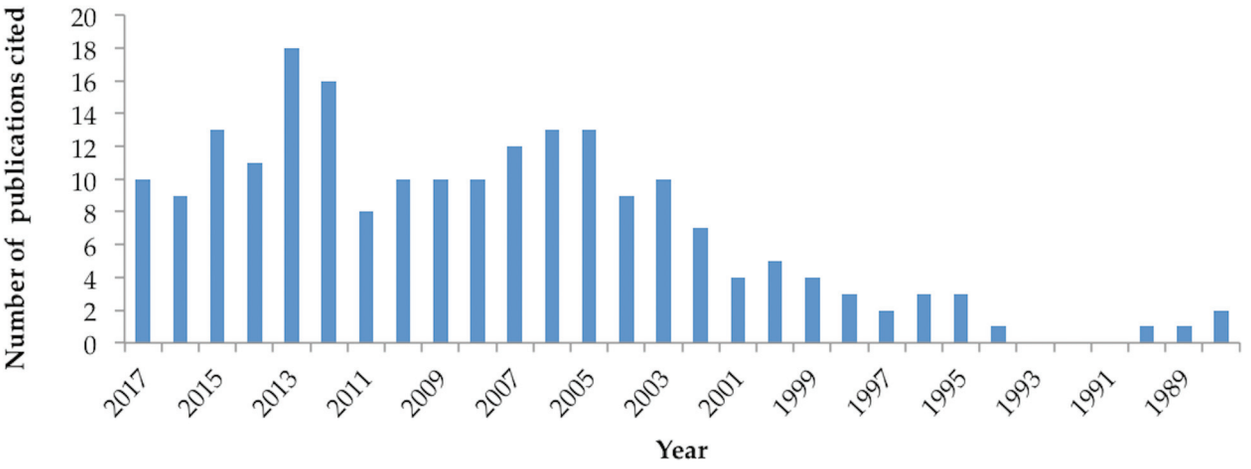

Figure 2. Number of publications cited per year.

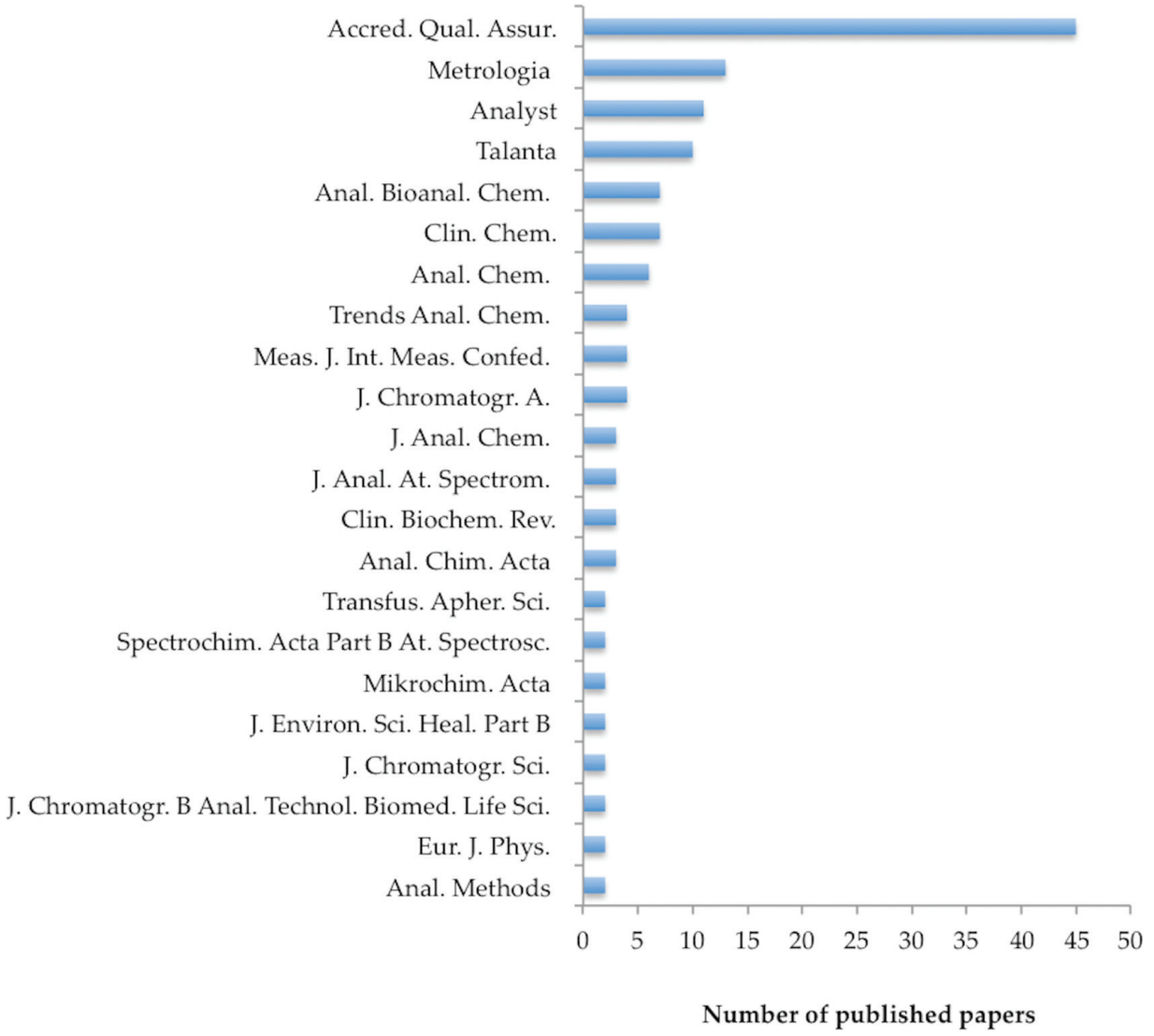

Figure 3. Number of papers cited by journals.

4. Final comments

Uncertainty is a measure of the quality of a measurement. It is of vital importance in many sectors of analytical chemistry to introduce quality control and quality assurance in production, complying with and enforcing laws and regulations; calibrating standards and instruments or developing and comparing international and national reference standards among others.

One of the best-known approaches to estimate the uncertainty of analytical procedures is the ISO/GUM. However, from an analytical viewpoint, this approach is sometimes tedious, time-consuming and unrealistic. One way to overcome these limitations is the procedure for evaluating uncertainty of analytical assays in routine analysis using the GUM approach together with the data from in-house validation based on the cause and effect diagram coming from the analytical specification function. Expressions to calculate the different contributions of uncertainty have to be carefully adapted in order to avoid double counting. The procedure is illustrated with a case study on fluorimetric determination of quinine in tonic water showing that it is very suitable for evaluating the uncertainty of the analyte content of future samples in routine analysis.

Finally, a summary including modern reviews on the estimation of measurement uncertainty of analytical assays by GUM is outlined in tabular form, which can be a useful guide for those interested in the subject. Moreover, selected application ranging from volumetric glassware, analytical balance, calibration curves, as well as the evaluation of the measurement uncertainty in classical and instrumental techniques in a wide variety of fields are given. Graphs on the number of references cited (over 200) per year and the number of papers by most cited journals are also included.

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